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The Research Grants Council of Hong Kong
NSFC/RGC Joint Research Scheme
Joint Completion Report

(Please attach a copy of the completion report submitted to the NSFC by the Mainland researcher)

Part A: The Project and Investigator(s)

1. Project Title

Development of Multifunctional Nanocomposite Particles for Imaging and Gene Therapy in Cancer Treatment

2. Investigator(s) and Academic Department/Units Involved

	Hong Kong Team	Mainland Team
Name of Principal Investigator *(with title)*	Professor Pei LI	Professor Yongsheng LI
Post	Professor	Professor
Unit / Department / Institution	Department of Applied Biology and Chemical Technology / The Hong Kong Polytechnic University	School of Materials Science and Technology / East China University of Science and Technology
Contact Information	pei.li@polyu.edu.hk	
Co-investigator(s) *(with title and institution)*	N.A.	Dr Niu Dechao / East China University of Science and Technology

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval *(must be quoted)*
Project Start date	1-Jan-2015	N/A	N/A
Project Completion date	31-Dec-2018	N/A	N/A
Duration *(in month)*	48	N/A	N/A
Deadline for Submission of Completion Report	31-Dec-2019	N/A	N/A

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1) Development of biocompatible bimetallic/polymer nanocomposite particles as dual-mode MR/CT contrast agents for tumor imaging;
2) Development of dual-functional core-shell nanocomposite particles for MR/CT imaging-guided gene therapy;
3) Development of intelligent nanocomposite particles for MR/CT imaging-guided gene therapy; and
4) Evaluation of intelligent nanocomposite system for MR/CT imaging-guided responsive (pH/temperature) gene therapy.

5.2 Revised Objectives
N.A.
Date of approval from the RGC: _____

Reasons for the change: _____

6. Research Outcome

Major findings and research outcome *(maximum 1 page; please make reference to Part C where necessary)*

1) A scalable synthesis of magnetic core–shell nanocomposite particles, acting as a novel class of magnetic resonance (MR) contrast agents, has been developed. Each nanocomposite particle consists of a biocompatible chitosan shell and a poly(methyl methacrylate) (PMMA) core where multiple aggregated γ-Fe_2O_3 nanoparticles are confined within the hydrophobic core. Their potential application as an MR contrast agent has been evaluated. Results show that the nanocomposite particles have good stability in biological media and very low cytotoxicity in both L929 mouse fi broblasts (normal cells) and HeLa cells (cervical cancer cells). They also exhibited excellent MR imaging performance with a T_2 relaxivity of up to 364 mM Fe^{-1} s^{-1}. An *in vivo* MR test performed on a naked mouse bearing breast tumor indicates that the nanocomposite particles can localize in both normal liver and tumor tissues. These results suggest that the magnetic core–shell nanocomposite particles are an efficient, inexpensive and safe T_2 -weighted MR contrast agent for both liver and tumor MR imaging in cancer therapy.
(*Part. Part. Syst. Charact.* **2016**, *33*, 756–763)

2) We have designed a new type of hybrid particles and evaluated its potential to be used in image-guided cancer diagnosis and therapy without the need of any toxic anticancer or contrast agents. The hybrid particles, consist of magnetic nanoparticles which are embedded in the poly(methyl methacrylate) (PMMA) cores and gold shells on chitosan (CTS). The potential application of the hybrid particles in tumor diagnosis and therapy was assessed *in vitro* and *in vivo* using 4T1 tumor cells and 4T1 tumor-bearing mice through combining magnetic targeting, photoacoustic (PA)/computed tomography (CT) imaging and photothermal therapy. Results
suggest that the hybrid particles can serve as a multifunctional tumor theranostic nanoplatform
for magnetically targeted photothermal therapy. Breast cancer has been effectively eliminated without the use of any anticancer drugs or contrast agents. Therefore, this type of core–shell hybrid particles represents a new composite particle design for effective and safe tumor theranostics. (*Journal of Biomedical Nanotechnology*, **2019,**15, 2072–2089)

3) We have developed a gene delivery system using polyethyleneimine (PEI)-based core–shell nanoparticles (PCNs) as gene delivery carriers, and investigated the effectiveness and safety for delivery of the shBMP-9 gene. The *In vitro* evaluation suggested that PCNs had

high loading capacity for exogenous genes and low cytotoxicity toward hepatocytes. The transfection
efficiency of PCNs/pENTR-shBMP9 complexes was higher than that of commercial lipofectamine 2000/shBMP9. In vivo studies showed that PCNs/pENTR-shBMP9 transfection led to a significant decrease in hepatic BMP9 expression compared with pENTR-shBMP9 transfection. Under high fat diet (HFD) feeding, Results suggest that the biological effects of PCNs/pENTR-shBMP9 *in vivo* are much more effective than those of pENTR-shBMP9. Therefore, the polyethyleneimine (PEI)-based core–shell nanoparticle can be applied as promising nanocarriers for effective and safe gene delivery. *(Nanoscale,* **2019**, 11, 2008–2016)

4) We have successfully synthesized water-dispersible and utrabright multi-carbon dot cross-linked polyethyleneimine (PEI) particles through self-assembly of hydrophobically modified PEI and in situ generations of carbon dots within residual monomer-swollen micelles. This type of multi-carbon dot cross-linked PEI particles possess synergistic photoluminescent effect of carbon dots and cross-linked PEI, giving high quantum yield (as high as 66%), multi-color emission, as well as pH- and photo-stable photoluminescence. The biological results demonstrate that the multi-carbon dot crosslinked PEI particles are promising intrinsic photoluminescent particles for image-guided diagnosis and therapy of cancer. (*Macromolecular Rapid Communication,* **(2019)**, 40, 1800869)

Potential for further development of the research and the proposed course of action *(maximum half a page)*

We have successfully designed and synthesized different types of hybrid particles and demonstrated their potential application for MR/CT dual-modality imaging, gene delivery and stimulus-response tumour therapy. In order to move the hybrid particles from the bench to the bedside, several experimental challenges need to be addressed. From a biological perspective, these include studies focused on understanding the *in vivo* fate and interactions of hybrid particles with the blood, tissue, cellular, and intracellular compartments in the host in healthy and diseased states. For hybrid particles to have clinical translation potential, the complexity in their design and development also needs to be minimized as much as possible to create systems that are able to be reproducibly prepared and characterized.

7. The Layman's Summary

(describe in layman's language the nature, significance and value of the research project, in no more than 200 words)

The use of nanotechnology in medicine has the potential to have a major impact on human health. To meet the demands for next-generation medical imaging, the development of safe and efficient dual-modality MR/CT contrast agents which can overcome inherent limitations in each imaging method and also provide complementary information for improved diagnosis and treatment is urgently needed. Furthermore, the development of multi-functional and intelligent nanoparticles that are capable of parallel detection, imaging and targeted therapy is the ultimate goal for future cancer treatment. In this project, we have designed and synthesized novel types of multi-functional nanocomposite particles for MR/CT dual-modality imaging, image-guided and stimulus-response tumor therapy. These All-In-One multiple purpose hybrid particles have been fabricated through a combination of superparamagnetic iron oxide nanoparticles with high saturation magnetization, gold nanoparticles, as well as pH-, temperature- and redox-responsive polymers. The novel multi-purpose nanomaterials developed in this project not only provide us with a new toolkit of next-generation nanomedicine for cancer detection and treatment, but also opens many new possibilities for the understanding of in-depth biochemical process.

Part C: Research Output

8. Peer-reviewed journal publication(s) arising directly from this research project

(Please attach a copy of each publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.)

The Latest Status of Publications				Author(s) ***(bold** the authors belonging to the project teams and denote the corresponding author with an asterisk*)*	Title and Journal/ Book *(with the volume, pages and other necessary publishing details specified)*	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
Year of publication	Year of Acceptance *(For paper accepted but not yet published)*	Under Review	Under Preparation *(optional)*						
2016				Lianghui Chen, **Dechao Niu** Cheng Hao Lee, Yuan Yao, Ki Lui, Kin Man Ho, **Pei Li***	Amphiphilic Core-Shell Nanocomposite Particles for Enhanced Magnetic Resonance Imaging *Part. Part. Syst. Charact.* **2016**, 33, 756–763	2016	Yes	Yes	Yes

2019				Jinfeng Liao, Yanpeng Jia, Lianghui Chen, Liangyu Zhou, Qiwen Li, Zhiyong Qian, **Dechao Niu**, **Yongsheng Li,** and **Pei Li***	Magnetic/Gold Core–Shell Hybrid Particles for Targeting and Imaging-Guided Photothermal Cancer Therapy *Journal of Biomedical Nanotechnology*, **2019** 15, 2072–2089,	2019	Yes	Yes	Yes
2019				Yanjun Jia, **Dechao Niu**, Qiujin Li, Hong Huang, Xinrun Li, Kejia Li, Ling Li, Cheng Zhang, Hongting Zheng, Zhiming Zhu,Yuan Yao, Xiaodong Zhao, **Pei Li*** and Gangyi Yang*	Effective gene delivery of shBMP-9 using polyethyleneimine-based core–shell nanoparticles in an animal model of insulin resistance *Nanoscale,* **2019**, 11, 2008–2016	2019	Yes	Yes	Yes

2019				Yuan Yao, **Dechao Niu**, Cheng Hao Lee, **Yongsheng Li, and Pei Li***	Aqueous Synthesis of Multi-Carbon Dot Cross-Linked Polyethyleneimine Particles with Enhanced Photoluminescent Properties *Macromolecular Rapid Communication,* **(2019)**, 40, 1800869				
			2019	Liangyu Zhou, Jinfeng Liao, Yanpeng Jia, **Dechao Niu, Yongsheng Li, Pei Li***	Temperature- and Magnetic-Sensitive Microgels for Imaging-Guided Therapy	No	No	Yes	

9. Recognized international conference(s) in which paper(s) related to this research project was/were delivered *(Please attach a copy of each delivered paper. All listed papers must acknowledge RGC's funding support by quoting the specific grant reference.)*

Month/Year/ Place	Title	Conference Name	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
April, 2015 Hangzhou, China	Amphiphilic Core-Shell Nanocomposite Particles with Magnetic-Cores for Enhanced Magnetic Resonance	ChinaNanomedicine 2015	2016	Yes	Yes	

October 2015 Kuala Lumpur, Malaysia	Novel Synthesis and Application of Metal/Polymer Core-Shell Nanocomposite Particles	The 4th Federation of Asian Polymer Societies – International Polymer Congress (4FAPS-IPC 2015)	2019	No	Yes	
Oct. 2016 Wuhan China	Amphiphilic Core-Shell Nanoparticles and Their Nanocomposites for Biological Applications	The 2st International Conference on Nanomedicine, China	2016	No	Yes	
Dec. 2016 Beijing, China	Novel Synthesis and Applications of Metal/Polymer Core-shell Nanocomposite Particles	The Second International Conference on Polymer Science and Engineering	2019	No	Yes	
Dec. 2017 Xiamen, China	Novel Synthesis and Applications of Metal/Polymer Core-shell Nanocomposite Particles	The 15th Pacific Polymer Conference	2019	No	Yes	
1-5 July 2018 Cairns, Australia	Synthesis of Multifunctional Nanocomposite Particles for Photothermal Therapy through Magnetic Targeting and Photoacoustic Imaging	World Polymer Congress Macro2018	2019	Yes	Yes	

September, 2018 Singapore	Amphiphilic Core-Shell Polymeric and Hybrid Nanoparticles in Biological Applications	The 1st Controlled Release Asia Meeting	2019	Yes	Yes	
15-17 Oct. 2018, Shanghai China	Multifunctional Hybrid Nanoparticles for Efficient Photothermal Therapy Through Magnetic Targeting and Photoacoustic/CT Dual-Modal Imaging	China Nanomedicine 2018	2019	Yes	Yes	

10. Student(s) trained *(Please attach a copy of the title page of the thesis.)*

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
Lianghui Chen	Ph.D.	23 August 2012	Graduated on 21 Sept. 2017

11. Other impact *(e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.)*

1. ACS Nano the Best Poster Award (2018)

Jinfeng Liao, Pei Li, et al, "Multifunctional Hybrid Nanoparticle Containing Magnetic Core and Gold Shell as a Theranostic Agent for Magnetic Targeting, PA/CT Dual-Modal Imaging and Photothermal Therapy" *China Nanomedicine 2018*, 15-17 Oct. 2018, Shanghai, China.

2. Collaboration with other research institutions

- State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China
- State Key Laboratory and Collaborative Innovation Center of Biotherapy, West China Hospital, Sichuan University, Chengdu, China
- Department of Endorinology, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, China.